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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ROBERT HEGER, HELMUT AUWETER,
JORG BREITENBACH, and HERIBERT BOHN

Appeal 2009-003678
Application 09/857,480
Technology Center 1600

Decided: August 18, 2009

Before ERIC GRIMES, LORA M. GREEN, and STEPHEN WALSH, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method of making a nanoparticulate composition and the composition itself. The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm-in-part.

STATEMENT OF THE CASE

The Specification discloses "nanoparticulate preparations of pharmaceutical active ingredients with a core/shell structure, where the active ingredient is present in the core in X-ray amorphous form together with at least one polymer, and the shell consists of a polymeric coating matrix" (Spec. 1).

Claims 15-21 and 23-27 are pending and on appeal. Claim 15 is representative and reads as follows:

Claim 15: A process for preparing a nano-particulate preparation of a pharmaceutical or cosmetic active ingredient with a core/shell structure, in which an X-ray amorphous active ingredient is present in the core together with one or more copolymers of acrylates, methacrylates, methacrylic acid or acrylic acid, and the shell consists of a stabilizing coating matrix, comprising

mixing an active ingredient/polymer solution or precipitate with an aqueous solution of a polymeric coating material continuously in a mixing chamber by spraying the two components as a compact jet into a mixing chamber

wherein said polymeric coating material is selected from the group consisting of gelatin, chitosan, alginates, casein, caseinates and homopolymers of acrylic acid, and

wherein the particle size of the core/shell structure is in the range of 0.05 to 0.9 μm.

The claims stand rejected under 35 U.S.C. § 103(a) as follows:

- claims 15-18 and 23-27 in view of Vallet Mas[1] and Redlich;[2]
- claims 19 and 20 in view of Vallet Mas and Weitschies;[3] and

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[1] Vallet Mas et al., EP 0 717 989 A1, June 26, 1996.
[2] Redlich et al., US 5,225,279, July 6, 1993.
[3] Weitschies et al., US 6,068,857, May 30, 2000.

- claim 21 in view of Vallet Mas and Liversidge.[4]

OBVIOUSNESS I

Issue

The Examiner has rejected claims 15-18 and 23-27 under 35 U.S.C. § 103(a) as obvious in view of Vallet Mas and Redlich. The Examiner finds that Vallet Mas "discloses a method of making … nanocapsules comprising a core and shell" that meets all the limitations of claim 15 except that Vallet Mas' core does not contain acrylate or methacrylate copolymers (Answer 3-4). The Examiner finds that Redlich "discloses core/shell particles comprising acrylate and methacrylate copolymers (abstract). … The core compris[es] methyl methacrylate (example 1)" (*id.* at 4). The Examiner concludes that a "skilled artisan would be motivated to include the methacrylate polymers in order to incorporate water-insoluble active agents such as isothiazolone" (*id.*).

Appellants contend that the Examiner erred in finding that the cited references suggest "an X-ray amorphous active ingredient" (Appeal Br. 6) and in finding that one of skill in the art would have been motivated to combine the acrylic polymers of Redlich with the process of Vallet Mas (*id.* at 9).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that one of skill in the art would have been motivated to combine the polymer coating procedure taught by Vallet Mas with the particles taught by Redlich and thereby arrive at

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[4] Liversidge et al., US 6,045,829, Apr. 4, 2000.

nanoparticles comprising an "X-ray amorphous active ingredient," as recited in claim 15?

Findings of Fact

1. Vallet Mas discloses a "process for the coating of droplets or particles with sizes below a micrometer, which contain, or are formed, of one or various chemical or biologically active substances" (Vallet Mas, 3: 8).

2. Vallet Mas discloses that "final product … is usable in any field, specially in the pharmacy and veterinary field" (*id.* at 3: 2-4).

3. Vallet Mas discloses that coated particles or droplets have "diameters comprised within 100 and 1000 nm, preferably within 200 and 500 nm" (*id.* at 3: 10-11).

4. Vallet Mas discloses that its

> process comprises: (1) preparing a fine dispersion of droplets or particles which contain or are formed of a chemical of biologically active substance in a phase comprised of a solvent and a non solvent of the polymer forming the coating …; (2) preparing a phase which contains the coat-forming polymer dissolved in a miscible solvent in any proportion with the prior dispersion; (3) mixing both phases continuously while … simultaneously spraying the resultant mixture in an evaporation system with temperature and vacuum conditions which provide for the instantaneous evaporation of the solvent from the polymer, causing the deposition of the polymer around the particles or droplets.

(*Id.*, abstract.)

5. Vallet Mas discloses that the particles coated "may be the actual active substance or have the active substance dispersed inside" (*id.* at 3: 15-16).

6. Vallet Mas discloses that the "phase which contains the coat-forming polymer … is prepared by disolving [sic] the coat-forming polymer in a solvent equal to the one used as part of" the active substance-containing phase (*id.* at 3: 21-22) and that the "solvent of the polymer may be for instance, an alcohol such as ethanol, methanol, [or] isopropanol" (*id.* at 3: 49).

7. Vallet Mas discloses that the polymer used to coat the particles can be "the acrylic acid copolymers and the acrylic polymer" (*id.* at 4: 11-13).

8. Redlich discloses a "process for preparing an aqueous dispersion of water-insoluble core/shell particles" (Redlich, col. 4, ll. 62-64).

9. Redlich discloses that an "oil-soluble initiator, a mixture of hydrophobic and hydrophilic solvents, anionic surfactant, and water-insoluble emulsion stabilizer are emulsified in water at high shear along with initial monomer … to form a 'core' emulsion" (*id.* at col. 5, ll. 34-40) and that the "core emulsion is then heated to polymerize the initial monomer" (*id.* at col. 5, ll. 52-53).

10. Redlich discloses that the "initial monomer includes … alpha, beta-ethylenically unsaturated carboxylic acid monomer" (*id.* at col. 5, ll. 48-52).

11. Redlich discloses that:

> Examples of nonionic monoethylenically unsaturated monomers which may be employed in preparing the core/shell particle includes …various (C_1 -C_{20}) alkyl or (C_3 -C_{20}) alkenyl esters of (meth)acrylic acid; for example, methyl methacrylate, methyl acrylate. ….
>
> Examples of alpha, beta-ethylenically unsaturated carboxylic acid monomer which may be used to prepare the core/shell

> particles include acid monomers such as methacrylic acid. … The preferred acid monomers that may be employed in preparing the core particles of the present invention are methacrylic acid and mixtures of acrylic acid and methacrylic acid, especially preferred is methacrylic acid.

(*Id.* at col. 7, ll. 6-42.)

12. Redlich discloses that "[w]hen it is desired to encapsulate an organic target material … the target material is included in the mixture which is sheared to yield the core emulsion" (*id.* at col. 5, ll. 40-46).

13. Redlich discloses that "[e]xamples of organic target materials which may be encapsulated by the process of the present invention include … pharmaceuticals" (*id.* at col. 11, ll. 29-40).

14. Redlich discloses that "[w]hen the polymerized dispersion is to ultimately be used to impart opacity, it is preferred that the average particle size of the core emulsion after dispersion be from about 0.22 to 0.35 microns" (*id.* at col. 9, ll. 34-36).

15. The Specification discloses that the

> active ingredient in the interior of th[e] core is present in X-ray amorphous form. It is essential that no crystalline active ingredient fractions are detectable (X-ray diffraction) in the active ingredient preparation. In particular, the polymers in the interior of the particles contribute to maintaining the active ingredient in its noncrystalline state.

(Spec. 4: 3-10.)

16. The Specification discloses that the polymer coating on the claimed nanoparticles "stabilize[s] the particles in their colloidal state so as to prevent heterogeneous particle growth (aggregation, flocculation etc.)" (*id.* at 3: 42-46).

17. The Specification states:

> Surprisingly, the colloidal active ingredient preparations according to the invention show distinctly less growth of hydrosol particles than known active ingredient preparations which consist essentially exclusively of active ingredient mass in the core of the colloidal particles. One hour after the aqueous hydrosols have been prepared in the presence of a solvent dissolving the active ingredient, the particle growth is a factor of 4 to 10 less. In the case of aqueous hydrosols which contain no solvent dissolving the active ingredient, the particle growth is reduced by a factor of 1.5 - 5.

(*Id.* at 3: 30-39.)

Principles of Law

"[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious," the answer depends on "whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007).

The obviousness analysis "can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 418.

Once the Examiner establishes that a product, recited in terms of its process of making, is prima facie unpatentable due to being in the prior art, Appellants bear the burden of proving "that the prior art products do not necessarily or inherently possess the characteristics of his claimed product." *In re Thorpe*, 777 F.2d 695, 698 (Fed. Cir. 1985) (quoting *In re Fitzgerald,* 619 F.2d 67, 70 (CCPA 1980); *In re Best,* 562 F.2d 1252, 1255 (CCPA 1977)).

"[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *In re Baxter-Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991).

"It is well settled that unexpected results must be established by factual evidence. Mere argument or conclusory statements in the specification does not suffice." *In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984).

Analysis

Claim 15 is directed to a process for preparing a nano-particulate preparation with an X-ray amorphous active ingredient in the core together with a copolymer of acrylates, methacrylates, methacrylic acid or acrylic acid, and a shell that can consist of homopolymers of acrylic acid.

Vallet Mas discloses a method of making coated particles having a diameter of 100-1000 nm (0.1-1 μm) by preparing a fine dispersion of droplets or particles comprising the active ingredient, and a phase that contains the coat-forming polymer (e.g., acrylic polymer), and spraying the two components together. Vallet Mas therefore discloses all of the limitations of claim 15 except for the presence in the core of a copolymer of "acrylates, methacrylates, methacrylic acid or acrylic acid" (claim 15).

Redlich discloses a process of making particles containing an organic target material (i.e., active ingredient) encapsulated in a polymer matrix. Redlich discloses that the core of its particles contains at least two polymerizable mono-ethylenically unsaturated compounds, which are preferably methacrylic acid and mixtures of acrylic acid and methacrylic acid.

In view of these disclosures, it would have been obvious to one of ordinary skill in the art to apply the Vallet Mas polymer coating procedure to the polymer/active ingredient particles of Redlich to obtain core/shell particles, with active ingredient in the core together with one or more copolymers of methacrylic acid or acrylic acid, and with a shell that contains homopolymers of acrylic acid. A person of ordinary skill in the art would have had reason to combine the disclosures of Vallet Mas and Redlich because Redlich teaches that its particles are useful for encapsulating organic materials including pharmaceuticals, and Vallet Mas teaches that its process begins with "droplets or particles which contain or are formed of a chemical of biologically active substance," including pharmaceuticals (FFs 4, 13). A skilled worker therefore would have considered it obvious to coat Redlich's particles using Vallet Mas' coating process.

Appellants argue that "the utilization of an active ingredient that is an X-ray amorphous active ingredient" is not disclosed by the cited references and is not inherent in them because the drug used in Vallet Mas' process in not necessarily amorphous (Appeal Br. 8).

This argument is not persuasive. First, neither Vallet Mas nor Redlich note any requirement for a crystalline active ingredient, and therefore would have made it obvious to use any, including noncrystalline (amorphous) active ingredients. In addition, the Specification distinguishes between active ingredients in X-ray amorphous form and "crystalline active ingredient fractions." Thus, the broadest reasonable interpretation of "amorphous form" would include active ingredient in any noncrystalline, including liquid, form. Given that both Vallet Mas and Redlich disclose

particles that comprise encapsulated droplets of active ingredient, the Examiner has reasonably established that the references suggest coated particles containing active ingredient in X-ray amorphous form.

Appellants further argue that "a skilled artisan had no apparent reason to modify the *Vallet Mas et al.* particles by incorporating polymeric materials used in the core of the *Redlich et al.* particles, because the *Redlich et al.* reference describes particles 'having a core containing a solvent blend.'" (Appeal Br. 9). Appellants also argue that the "proposed combination would involve not mere modification of, but complete abandonment of the principle of operation (sequential microsuspension polymerization) of the *Redlich et al.* process" (*id.* at 8).

This argument is not persuasive. As discussed above, the combination of the references suggests forming particles according to the procedures described in Redlich, and coating the particles using the coating method of Vallet Mas. Such a combination is no more than the predictable use of prior art products and processes according to their established functions.

Appellants also argue they have made a showing of unexpected results for the claimed invention because the Specification discloses that particles having a core of active ingredient/polymer showed greater particle size stability than particles having a core of active ingredient alone (Appeal Br. 12).

This argument is not persuasive. Unexpected results must be shown to be unexpected when compared with the closest prior art. Here, Appellants have stated that "aqueous hydrosols … prepared in the presence of a solvent dissolving the active ingredient" showed surprisingly less

growth in particle size compared to "aqueous hydrosols which contain no solvent dissolving the active ingredient" (FF 17). Appellants, however, have provided no evidence to support the conclusory statement in the Specification, nor have they provided a comparison to the particles disclosed by either Redlich or Vallet Mas. "It is well settled that unexpected results must be established by factual evidence. Mere argument or conclusory statements in the specification does not suffice." *In re De Blauwe*, 736 F.2d at 705.

With regard to claims 16 and 17, Appellants argue that the cited references do not disclose the additional limitation of those claims (Appeal Br. 9). The Examiner finds that the suggested "core/shell nanoparticles … would inherently comprise phases with and without drug since the cores comprise active agents in addition to polymers forming areas of drug and areas of polymer" (Answer 4).

Appellants' arguments are persuasive. Claims 16 and 17 require that the core has at least two separate phases. While we agree with the Examiner that Vallet Mas and Redlich suggest nanoparticles that contain X-ray amorphous active ingredient and polymer, the Examiner has not adequately shown that the resulting product would inherently comprise a phase that consists of "amorphous particles of active ingredient" separate from a phase that is a dispersion of active ingredient in a polymer matrix (claim 16), or a phase that consists of amorphous active ingredient in a phase separate from a polymer matrix free of active ingredient (claim 17).

Appellants also argue that the cited references do not disclose the additional limitations of claims 18, 23-25, and 27 (Appeal Br. 9-10).

These arguments are not persuasive. With respect to claim 18, both Vallet Mas and Redlich suggest that the disclosed nanoparticles are suitable for pharmaceutical applications. In addition, Redlich discloses core polymers that are methacrylic acid or mixtures of acrylic acid and methacrylic acid, which are encompassed by claim 15 (from which claim 18 depends). Appellants have provided no evidence that the polymers disclosed by Redlich do not meet the limitations of claim 18.

With respect to claim 23, the Examiner finds that a hydrosol is produced during Vallet Mas' process (Answer 4), and Appellants have provided no basis on which to conclude that the Examiner's finding is incorrect.

With respect to claim 24, the nanoparticles disclosed in the instant Specification and the nanoparticles suggested by the prior art have a coating of the same polymer surrounding a core that is the same combination of active ingredient and core polymer, and are made by the same process. Therefore, the Examiner has established a reasonable basis for concluding that the nanoparticles suggested by the prior art would have similar properties to those disclosed in the instant Specification. Appellants have not provided any evidence to show that they would not.

With respect to claim 25, Vallet Mas discloses that its two phases include the same solvent and that the solvent can be "an alcohol such as ethanol, methanol, isopropanol," etc. (FF 6). Appellants have provided no evidence that the solvents disclosed by Vallet Mas do not meet the limitations of claim 25.

With respect to claim 27, the nanoparticles suggested by the prior art reasonably appear to be identical to the instantly claimed nanoparticles, and are made by the same process. Therefore, the Examiner has established a reasonable expectation that the nanoparticles suggested by the prior art and instantly claimed nanoparticles would have similar properties. Appellants have not provided any evidence to the contrary.

Conclusions of Law

The evidence of record supports the Examiner's conclusion that one of skill in the art would have been motivated to combine the acrylic polymers of Redlich with the process of Vallet Mas, and that the combination would have suggested the limitations of claims 15, 18 and 23-25, and 27. Claim 26 has not been argued separately and therefore falls with claim 15. 37 C.F.R. § 41.37(c)(1)(vii).

The evidence of record does not support the Examiner's conclusion that Vallet Mas and Redlich would have suggested the process of claims 16 and 17.

OBVIOUSNESS II

Issue

The Examiner has rejected claims 19 and 20 under 35 U.S.C. § 103(a) as being obvious in view of Vallet Mas and Weitschies.

The Examiner finds that, in addition to the disclosures discussed above, Vallet Mas "teaches that natural copolymers can be used in the coating phase of the formulation" (Answer 5). The Examiner finds that Weitschies "discloses a nanoparticle formulation comprising a core/shell

structure," and that the "shell phase can comprise a wide range of natural materials and their derivatives such as gelatin, albumin," etc. (*id.* at 5-6). The Examiner concludes that it "would have been obvious to one of ordinary skill in the art … to combine the natural polymers of [Weitschies] as suggested by [Vallet Mas] in order to provide stability and structural integrity to the nanoparticle formulation" (*id.* at 6).

Appellants argue that the cited references fail to suggest the claim limitation that "the polymer in the active ingredient/polymer solution is one or more copolymers of acrylates, methacrylates, methacrylic acid or acrylic acid" (Appeal Br. 10).

Appellants' arguments are persuasive. Claims 19 and 20 depend from independent claim 15, which requires that the "active ingredient is present in the core together with one or more copolymers of acrylates, methacrylates, methacrylic acid or acrylic acid." Given that the Examiner has not indicated where either Vallet Mas or Weitschies disclose or suggest the required copolymer in the core, the Examiner has not adequately explained how the cited references disclose or suggest the methods of claims 19 and 20.

OBVIOUSNESS III

Issue

The Examiner has rejected claim 21 under 35 U.S.C. § 103(a) as being obvious in view of Vallet Mas and Liversidge.

The Examiner relies on Vallet Mas as discussed above. The Examiner finds that Liversidge "discloses a nanoparticle formulation where the surface of the shell are stabilized by the inclusion of natural polymers such as gelatin, lecithin and casein" (Ans. 6), and concludes that it "would have been

obvious to combine the stabilizers of [Liversidge] in to the process of [Vallet Mas] in order to improve the surface stability of the nanoparticle formulation" (*id.* at 7).

Appellants argue that the cited references fail to suggest the claim limitation that "the polymer in the active ingredient/polymer solution is one or more copolymers of acrylates, methacrylates, methacrylic acid or acrylic acid" (Appeal Br. 11).

Again, Appellants' arguments are persuasive. Claim 21 depends from independent claim 15. Given that the Examiner has not indicated where either Vallet Mas or Liversidge disclose or suggest "one or more copolymers of acrylates, methacrylates, methacrylic acid or acrylic acid" in the core, as required in claim 15, the Examiner has not adequately explained how the cited references disclose or suggest the invention of claim 21.

SUMMARY

We affirm the rejection of claims 15, 18, and 23-27 under 35 U.S.C. § 103(a) as obvious in view of Vallet Mas and Redlich. However, we reverse the rejection of claims 16, 17, and 19-21.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED-IN-PART

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